REMARKS / ARGUMENTS

In the Office Communication dated March 28, 2006, the Examiner suggests that not all points raised in the previous Office Action dated as of July 21, 2005 were satisfactorily addressed in the Applicant's response of 18 November and 16 December 2005, respectively. In accordance with the Examiner's request, the Applicant provides further comment below.

The Examiner has rejected claims 1-6 and 11-12 under 35 U.S.C. § 112, first paragraph as failing to comply with written description requirement. Specifically, in the Examiner's view, a true assessment of patentability cannot be made because the data presented in Figures 3 and 4 allegedly do not confirm whether the Applicant was in possession of a method of diagnosing Alzheimer's Disease (AD) based on a specific defect in the cell cycle. The Examiner states that due to an alleged lack of differences shown between the results presented in Figure 3 and the results in Figure 4, it is not clear that Alzheimer's Disease could be diagnosed based on a specific cell cycle defect. The Applicant submits that the consideration of the data presented in Figure 3 and Figure 4 in isolation may not be solely dispositive of the issue of whether the Applicant was in possession of the invention at the time of filing. However, notwithstanding the results presented in Figures 3 and Figure 4, possession of the invention as detailed in the above-referenced claims was adequately shown by the results of Figure 2 and Figure 5. Specifically, the Applicant was clearly in possession of a method of diagnosing Alzheimer's Disease based upon a defect in the cell cycle as detailed below.

In the experimental section of the application, beginning on page 23 in Example 1, two separate sets of studies were described. In the first set of studies, carried out on 49 subjects as identified in Table 1a on page 27, two lymphocyte samples from each subject were treated with phytohaemaglutinin (PHA) and then one sample treated with rapamycin (a specific G1 inhibitor) while the other untreated culture was kept as a control. After a further 23 hours, BrdU was added to both samples. BrdU incorporation was assessed using immunochemistry and flow cytometry. Flow cytometry is the gold standard in the field for measuring cell cycle effect and alterations and is regarded as both sensitive and accurate.

In these studies, differences in the relative length of the G1 phase manifested as between control cells and patient samples on treatment with rapamycin was established as represented graphically in Figure 2. As shown in Figure 2, the relative lengthening of G1 was significantly reduced in AD (with or without other pathologies; AD and ADM group) as well as in the preclinical stages of Alzheimer's disease (pre AD group) relative to controls and other dementias (DNOS). Thus, based upon the first set of studies as shown in Figure 2, it was clear the Applicant was in possession of a method of diagnosing Alzheimer's disease based upon a G1/S regulatory failure, irrespective of what is shown in the second set of experiments. In respect of these, however, a discussion of their relevance is also provided.

The second set of studies are very different in nature from the first set of studies discussed measurements of a different outcome of cell cycle manipulation were obtained at different check points. Four lymphocyte cultures were set up in respect of each of 53 subjects as shown in Table 1b on page 27. Control cultures were left without any treatment while each of the other three were tested using rapamycin, doxorubicin and H_2O_2, respectively. Doxorubicin induces DNA damage, leading to arrest in G2/M rather than G1/S. H_2O_2 treatment produces oxidative stress, leading to a reversible and temporary cell cycle in G1/S. Thus, the H_2O_2 treatment is akin to rapamycin in its effect. Following incubation, the outcome of cell cycle manipulation was measure not by flow cytometry but by measuring cell survival using the MTT cell survival assay. The MTT assay is an assay that measures mitochondrial enzyme activity as an indication of surviving cells. This measure can be used for the rough estimation of cell numbers because every living cell has roughly the same amount of active mitochondrial I enzyme, unless number of mitochondrial is affected adversely by a disease state.

The results of this second set of studies are shown in Figures 3, 4 and 5, respectively. These results confirm that MTT is a rather more rough guide to cell cycle effects than flow cytometry. Nevertheless, use of the MTT method demonstrated differences in behavior at the G1/S checkpoint between control and patient groups. This observation is clearly shown in Figure 5 where differences between AD or potential AD patients and controls or DNOS patients were demonstrated. The reduction in cell numbers by H_2O_2 was dependent on clinical diagnosis. H_2O_2 resulted in low cell numbers (strong cell cycle

inhibition) in controls but a significantly bigger cell population in pre-AD and AD patients (poor cell cycle control) was shown. Further, this was in contrast to the results obtained with doxorubicin, the G2/M inhibitor. Here the data in Figure 4 show detection of an age-dependent G2 problem when doxorubicin is used but this is not surprising because in lymphocytes, G2 is controlled by the same molecules as the G1/S transition. It is not relevant for AD because neurons never pass this control anyway. However, the differences between the doxorubicin experiment and the H_2O_2 experiment are different enough to exclude that the effects seen are non-specific effects due to pre-existing DNA damage, rather than just similar control mechanisms affecting two different check points.

The Applicant demonstrated the ability to detect AD-type G1/S transition defects (that lead to AD type pathology and neurons) from lymphocytes in the specification as originally filed. As such, the subject matter of the invention as defined in claims 1-6 and 11-12 is well supported by the rapamycin results measured by flow cytometry shown in Figure 2 and the H_2O_2 data measured by the MTT assay shown in Figure 5. Accordingly, the Applicant respectfully requests reconsideration and withdrawal of the Examiner's rejection of claims 1-6 and 11-12 under 35 U.S.C. § 112, first paragraph.

CONCLUSION

On the basis of the foregoing amendments, Applicants respectfully submits that the pending claims are in condition for allowance and respectfully request the same. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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